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Award Number: DAMD17-01-1-0537

TITLE: Premenopausal Levels of Circulating Insulin-Like Growth Factor I and the Risk of Post-Menopausal Breast Cancer: a Population-Based, Nested Case-Control Study

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REPORT DATE: June 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	June 2002	Annual (15 May 01 - 14 May 02)

4. TITLE AND SUBTITLE
Premenopausal Levels of Circulating Insulin-Like Growth Factor I and the Risk of Post-Menopausal Breast Cancer: a Population-Based, Nested Case-Control Study

5. FUNDING NUMBERS
DAMD17-01-1-0537

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

High levels of circulating IGF-1 may be a risk factor for breast cancer. Only one population-based epidemiologic study of IGF-1 and breast cancer measured circulating IGF-1 in serum drawn prior to diagnosis. For post-menopausal breast cancer cases, no association was found. However, these analyses did not include IGF-1 measures from the pre-menopausal period when endogenous IGF-1 exposure is naturally higher and, potentially, more predictive of breast cancer risk. This study is a nested case-control analysis of archived serum samples and existing questionnaire data from the CLUE studies. 5,290 women participated in the prospective CLUE studies -- 129 developed a first, incident invasive breast cancer between 1990 and 1998. Cases diagnosed premenopausally will be excluded. One control will be matched to each case on age, menopausal status, age at menopause, follow-up time, date of each blood draw. Samples will be sent to the lab of Dr. Michael Pollack at McGill University. Plasma IGF-1 and IGFBP-3 concentrations will be determined by enzyme-linked immunoabsorbent assay (ELISA). Statistical analyses will: 1) estimate the association between premenopausal IGF-1 levels (with and without adjustment for IGFBP-3) on postmenopausal breast cancer risk; and 2) determine whether this association differs from that for postmenopausal IGF-1 levels.

14. SUBJECT TERMS	15. NUMBER OF PAGES
breast cancer, IGF-1, menopause	5
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Introduction

The specific aim of this Concept Project is to determine if the level of insulin-like growth factor 1 (IGF-1) measured in serum samples taken before menopause associated with the risk of breast cancer after menopause. IGF-1 is a naturally occurring polypeptide, part of a complicated system of hormones, binding proteins, and receptors referred to as the "growth hormone/IGF axis." IGF-1 plays a role not only in the normal development of breast tissue but also in the proliferation of epithelial cells in the mature breast which, in turn, increases the chances of neoplastic transformation. The circulating levels of IGF-1 in the blood vary widely across women and these levels increasingly are believed to correlate well with IGF-1 activity in target epithelial tissue. Consequently it has been hypothesized that high levels of circulating IGF-1 may be a risk factor for breast cancer. Only two population-based epidemiologic studies of IGF-1 and risk of invasive breast cancer have been conducted to date. Just one, a case-control comparison nested within a prospective cohort study, measured circulating IGF-1 in serum drawn prior to diagnosis. Findings in this study, along with those from a few small non-population-based case-control studies, indicate a strong association between IGF-1 levels and breast cancer diagnosed before menopause. No association was detected between available IGF-1 measures and breast cancer diagnosed after menopause. IGF-1 is a naturally occurring polypeptide, part of a complicated system of hormones, binding proteins, and receptors referred to as the "growth hormone/IGF axis." IGF-1 plays a role not only in the normal development of breast tissue but also in the proliferation of epithelial cells in the mature breast which, in turn, increases the chances of neoplastic transformation. The circulating levels of IGF-1 in the blood vary widely across women and these levels increasingly are believed to correlate well with IGF-1 activity in target epithelial tissue. Consequently it has been hypothesized that high levels of circulating IGF-1 may be a risk factor for breast cancer. Only two population-based epidemiologic studies of IGF-1 and risk of invasive breast cancer have been conducted to date. Just one, a case-control comparison nested within a prospective cohort study, measured circulating IGF-1 in serum drawn prior to diagnosis. Findings here, along with those from a few small non-population-based case-control studies, indicate a strong association between IGF-1 levels and breast cancer diagnosed before menopause. No association was detected between available IGF-1 measures and breast cancer diagnosed after menopause.

This study is a nested case-control analysis of archived serum samples from the CLUE serum bank and existing questionnaire data for each case and control. A total of 5,290 women participated in CLUE prospective studies -- with 129 developing a first, incident invasive breast cancer between 1990 and 1998. Cases diagnosed premenopausally will be excluded. One control will be matched to each case on age, menopausal status, age at menopause, follow-up time, date of each blood draw (within one month), and, consequently, time from each blood draw to menopause. Controls with a history of cancer at any site will be excluded. Samples will be sent to the lab of at McGill University. For each of sample, plasma IGF-1 and IGFBP-3 concentrations will be determined by enzyme-linked immunoabsorbent assay (ELISA). IGF-1 and IGFBP-3 levels will actually be measured twice for each sample and each sample's mean will be the value used in the statistical analysis. Statistical analyses will: 1) estimate the association between premenopausal IGF-1 levels (with and without adjustment for IGFBP-3) on postmenopausal breast cancer risk; and 2) determine whether this association differs from that for postmenopausal IGF-1 levels. IGF-1 measures will be considered alternatively as continuous and categorical variables. Conditional logistic regression models will be employed with generalized estimating equation (GEE) algorithms used to account for within-individual correlation of IGF-1 measures.

Report Body

Although the official funding period for this project began May 15, 2001 because it took a considerable amount of time for the project to clear Human Subjects Protection review, the authorization to begin the work was not received until October of 2001. Following that authorization the following steps have been completed:

- The CLUE database was queried to select eligible cases and controls. Because follow-up for cancer status in the CLUE population has been extended through 2000 (at the time the proposal was written, follow-up was available only through 1998), our sample size is larger than anticipated - 127 cases plus controls. In addition, approximately 20% of the case group had two premenopausal samples available (these subjects participated in 1974 and 1989 blood draw and were still premenopausal in 1989 but then had postmenopausal breast cancer diagnosis before 2000).
- ID numbers were sent to the Washington County Public Health Training Center for the sample aliquots to be drawn and shipped to the laboratory at McGill in Montreal.
- Samples were sent to McGill in the Spring of 2002. (We expect assays to be completed by the end of the Summer of 2002.)
- An analytic data file has been readied, comprising questionnaire data on potential covariates (breast cancer risk factors) for cases and controls (this will be linkable to assay results by the study ID numbers)

Key Accomplishments

Research is still in the implementation phase, as described above.

Reportable Outcomes

None.

Conclusions

None yet.

References

NA

Appendices